Remarks

Claims 1-8, 10-13, and 16-22 were pending in the subject application. By this Amendment, claims 1, 2, 5, 6, 10, 11, and 17-21 have been amended, claim 22 has been cancelled, and new claims 24-26 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicant's agreement with or acquiescence in the Examiner's position. Accordingly, claims 1-8, 10-13, 16-21, and 24-26 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, claims 1, 5, 10, and 17 have been amended to recite that the particle comprises a complex of chitosan, or a chitosan derivative, a lipid, and a polynucleotide. Support for this amendment may be found, for example, at page 8, lines 4-13, of the specification. Support for claim 24 can be found at page 17, lines 1-11, and Example 2, of the specification. Support for claims 25 and 26 can be found, respectively, at page 11, lines 13-17, and page 10, lines 10-30, of the specification.

Claims 1-8, 10-13, and 16-22 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicant respectfully submits that the specification sets forth the claimed invention in such full, clear, concise, and exact terms so as to show possession of the claimed invention.

Under U.S. patent law, there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 521, F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Information which is well known in the art need not be described in detail in the specification. See, *e.g.*, *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-1380, 231 USPQ 81, 90 (Fed. Cir. 1986). If a skilled artisan would have understood the inventor to be in possession of the invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then an adequate written description requirement is met. See, *e.g.*, *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111. 1116 (Fed. Cir. 1991). Moreover, a specification need not necessarily describe how to make and use every

embodiment of the invention, because the artisan's knowledge of the prior art and routine experimentation can often fill in gaps." *Liebel-Flarsheim Co. v. Medrad*, WL 851205 at 8 (Fed. Cir. 2007), citing *AK Steel Corp. v. Sollac & Ugine,* 344 F.3d 1234, 1244 (Fed. Cir. 2003). However, in this case, the meaning of what constitutes a "chitosan derivative" is already provided at page 10, line 10, through page 11, line 12, of the specification. Thus, a person of ordinary skill in the art would understand the meaning of the term. Moreover, numerous examples of chitosan derivatives that may be used for forming the particles recited in the claims are well known to a person of ordinary skill in the art. For example, U.S. Patent No. 5,840,341 (Watts *et al.*) a patent issued before the filing of this patent application, claims drug-delivery compositions containing chitosan derivatives and, at column 6, lines 25-33, notes that chitosan derivatives can "include ester, ether or other derivatives formed by interaction of acyl or allyl groups with the OH groups and not the NH_2 groups." Additionally, the Watts *et al.* patent teaches examples such as O-alkyl ethers of chitosan and O-acyl esters of chitosan. U.S. Patent No. 6,458,938 (Cha *et al.*) describes examples of chitosan derivatives conjugated to polyethylene glycol, as mentioned by the applicant. Another issued patent, U S. Patent No. 6,887,564, which claims articles containing chitosan materials, provides examples of chitosan derivatives, in column 10, lines 33, through column 11, line 60. Thus, a person of ordinary skill in the art would understand the meaning of the term "chitosan derivative" and immediately envision representative examples of chitosan derivatives. Furthermore, submitted herewith for the Examiner's consideration is a copy of Liu and Yao (*J. Controlled Release*, 2002, 83:1-11), which describes a variety of chitosan derivatives known in the art. The applicant was in possession of the claimed genus of chitosan derivatives at the time the application was filed. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 10-13 and 16-22 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully submits that the claimed subject matter as currently amended is fully enabled by the subject specification.

The Office Action acknowledges that the subject specification provides enablement for delivery of a polynucleotide to a host. However, the Office Action indicates that the specification does not provide enablement for sustained *in vivo* gene delivery for the purpose of treating a disease

state in a human host. As stated in MPEP 2164.04, the Examiner should always look for enabled, allowable subject matter and communicate to the applicant what that subject matter is at the earliest point possible in the prosecution of the application.

By this Amendment, the applicant has amended claims 10 and 17 to recite that the particle is administered to a mammal. The experimental evidence in the subject specification supports the enablement of the methods recited in the claims as currently amended, *e.g.*, delivery and expression of a polynucleotide within a mammal (claim 10), and enhancing interferon-gamma expression to regulate the production of cytokines secreted by T-helper type 2 (Th2) cells within a mammal (claim 17). Examples 2-4 of the specification describe experiments demonstrating intranasal delivery and expression of a polynucleotide in mouse lung (pages 26-29; Figures 3A-3C; Figure 4). Figure 5C shows that the particles comprising a complex of chitosan and an IFN-gamma-encoding polynucleotide rapidly induced IFN-gamma expression, before leveling off, for example.

Furthermore, the particles of the invention induce significantly less IL-6 (a marker of acute inflammation) compared to that induced by chitosan, which is particularly relevant for clinical applications in human subjects. Figure 4 shows decreased IL-6 levels, as compared to the control, as described in Example 4 at page 29, lines 1-10, of the specification.

In addition, as shown in Figure 6B, and described in Example 6 (page 31, lines 9-21) of the specification, mice treated with particles comprising chitosan and an IFN-gamma-encoding polynucleotide showed significantly attenuated airway hyperresponsiveness. Figure 6C shows that there was a significant reduction in the number of eosinophils in the lungs. As indicated at page 3, line 28, through page 4, line 13, interferon-gamma is a desirable candidate for asthma therapy because of its capacity to reduce IL-13 induced eosinophilia.

Additionally, as shown in Figure 8D, analysis of cytokine secretion from splenocytes shows that there was an increase in interferon-gamma production and a decrease in IL-4 and IL-5 in the mice treated with particles comprising chitosan and an IFN-gamma-encoding polynucleotide, as compared to the controls. Thus, the numerous examples show successful modulation of cytokines.

Furthermore, the applicant respectfully submits that the Examiner mischaracterizes the state of the art at the time the subject application was filed. The Verma and Eck references are both more than ten years old and primarily emphasize viral vectors. New techniques in gene therapy involving

other delivery mechanisms are not even mentioned. Moreover, gene therapy is a very broad term. For example, the American Society of Gene Therapy defines gene therapy as an "approach to treating disease by either modifying the expression of an individual's genes or correction of abnormal genes." Thus, therapeutic success is dependent on the type of delivery mechanism used.

The applicant recognizes these differences and notes that, at page 35, lines 9-18, the subject specification indicates that the "reduction in eosinophilia was greater with CIN therapy than using adenovirus-IFN treatment" and that CIN therapy works effectively and rapidly, despite producing 10-fold less interferon-gamma than adenovirus-mediated IFN-gamma transfer. These results are indicative of superiority over the adenoviral vectors discussed within the references cited in the Office Action, and over cationic lipids and cationic polymers alone, particularly in view of the fact that these compounds, when administered alone, had generally lower transfection efficiency of viral vectors, as mentioned in the background section of the subject application.

With respect to the animal model, the applicant submits that all that is required by the patent laws is that a "reasonable correlation" exists between the scope of the claims and the scope of enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985). MPEP 2164.02 states that an animal model constitutes a working example if the example correlates with a disclosed or claimed method invention. The mouse model is a well-known animal model for studying disease in humans. Accordingly, through the examples provided in the specification, the applicant has demonstrated that the method of the invention results in gene expression *in vivo* using an art-recognized animal model. One of ordinary skill in the art would conclude that the experiments described in the specification are reasonably predictive of gene expression in mammals as a whole.

In addition, compliance with the enablement requirements of 35 U.S.C. §112, first paragraph, does not turn on what type of example is disclosed (See MPEP 2164.02). Thus, the mere fact that the application does not contain working examples with human asthmatic patients is not determinative. Prophetic examples and other guidance may also satisfy the enablement requirement.

Therefore, the applicant respectfully submits that, given the teachings of the specification, one of ordinary skill in the art could carry out the claimed method without the need for undue

experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1, 3-5, 7, 8, 10, 12, 13, 16-18, 20, and 21 have been rejected under 35 U.S.C. §102(b) as being anticipated by Truong *et al.* (WO 99/36089). The applicant respectfully submits that the Truong *et al.* publication does not teach the particles or methods of the invention.

By this Amendment, the applicant has amended claims 1, 5, 10, 17, and 21 to recite that the particle comprises a lipid. As the Examiner is aware, to be anticipatory under 35 U.S.C. §102, a reference must disclose each and every element as set forth in the claim, either expressly or inherently. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Truong *et al.* publication does not teach or suggest a particle comprising chitosan, or a chitosan derivative, a polynucleotide, and a lipid; or methods of using and making such particles. Thus, there is no anticipation.

With respect to claim 17, it is well known that interferon-gamma promotes a Th1 response, which down-regulates the Th2-like immune response that is the hallmark of allergic diseases, including asthma. Example 4 of the Truong *et al.* publication relates to shifting to a Th2 response, rather than a Th1 response, and teaches away from the claimed methods.

As described in Example 4 of the subject application (page 28, lines 13-31, and page 29, lines 1-10), it was unexpected that the particles incorporating a lipid (chlipids) induced significantly less IL-6 (a marker of acute inflammation) compared to particles without the lipid. In addition, the complex of chitosan, lipid, and polynucleotide take advantage of electrostatic interactions between the cationic properties of chitosan, lipid, and the anionic properties of a polynucleotide. The claims are neither anticipated nor obvious in view of the Truong *et al.* publication. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 1-8, 10-13, and 16-22 have been rejected under 35 U.S.C. §102(e) as being anticipated by Ni *et al.* (published U.S. application 2002/0151009). The applicant respectfully submits that the Ni *et al.* publication does not teach or suggest the particles and methods recited in the claims as currently amended.

As indicated above, by this Amendment, the applicant has amended claims 1, 5, 10, 17, and 21 to recite that the particle comprises a complex of chitosan, or a chitosan derivative; a lipid; and a

polynucleotide. At page 13, lines 3-9, the Office Action indicates that the Ni *et al.* publication teaches

> ...formulations comprising nucleic acids and chitosan and combinations and mixtures of other materials (page 113, parag. 1032) ... formulations comprising nucleic acids and biodegradable polymer (chitosan) may also include release-rate modification agents and/or pore-forming agents ... including fatty acids (lipids) (page 113, parag. 1034). Ni *et al.* teach a variety of liposomes (page 56, parags. 0537-0538).

The Ni *et al.* publication simply indicates that the "formulations" may include "fatty acids"; that chitosan is an example of a biodegradable polymer that can be used in the formulation of compositions; and that polynucleotide constructs can be complexed in a "liposome preparation." Moreover, Ni merely teaches that fatty acids and chitosan are among many of the laundry list of agents that can be used in the formulation of compositions.

The Ni *et al.* publication does not teach or suggest a particle comprising chitosan, or a derivative thereof, a polynucleotide, and a lipid, or methods of using and making such particles. Thus, there is no anticipation. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The elements must be arranged as required by the claim (MPEP §2131). For the same reasons discussed with respect to the Truong *et al.* publication, the claims are neither anticipated nor obvious in view of the Ni *et al.* publication. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

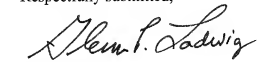
Claims 10-13, 16-18, and 20 have been provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 1-3, 9, 10, 13, and 15-18 of co-pending Application No. 11/117,169. The applicant respectfully asserts that the claims as currently amended are not obvious over the claims of the cited patent application. By this Amendment, the applicant has amended claims 10 and 17 to recite that the particles comprise a lipid. The applicant intends to cancel claim 10 of co-pending Application No. 11/117,169. As the double patenting rejection is a provisional rejection, the applicant requests that the rejection be held in abeyance until claim 10 of the co-pending application is cancelled or such time that the subject application is otherwise determined to be in condition for allowance.

Claims 2-4 depend from claim 1; claims 6-8 depend from claim 5; claims 11-13, and 16 depend from claim 10; and claims 18-20 depend from claim 17, respectively. These dependent claims incorporate all of the limitations of the base claims and additional limitations. Therefore, claims 1-8, 10-13, and 16-21, and new claims 24-26, are now in condition for allowance.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Amendment Transmittal Letter
Liu and Yao (*J. Controlled Release*, 2002, 83:1-11)